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ORIGINAL ARTICLE

Diarrhea-associated micronutrient deficiencies and risk of subsequent diarrhea in admitted children to Hajar hospital in Shahrekord, Iran

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ABSTRACT

Background: Acute infectious diarrhea is still one of the most important causes of death in childhood and malnutrition increases its morbidity and mortality. There is a strong correlation between the nutritional status of the child and the risk of subsequent diarrhea. Micronutrient deficiencies also increase the child's susceptibility to diarrhea and vitamin A and zinc supplementation has been shown to reduce the incidence and hasten recovery from acute diarrhea episodes.

Materials and methods: This study describes the association of nutritional deficiencies and other factors on the risk of subsequent diarrhea in children in Shahrekord, Iran. A cohort of 211 children less than 5 years old admitted with acute diarrhea to Hajar Hospital in Shahrekord, were followed for 14 weeks after hospital discharge.

Results: Fifty-eight (27%) of these children developed a new diarrhea episode during the follow up period. Children who were vitamin A and zinc deficient at the time of admission, above 12 months of age, kept animals at home or had weight-for-age and weight-for-height z scores <-1 during the univariate analysis had a higher risk of experiencing subsequent diarrhea. Vitamin A and zinc deficiencies, keeping animals at home, diarrhea duration ≤ 4 days on enrolment and weight-for-age z score <-1 reminded as independent risk factors during multivariate analysis. The aggregation of these factors had a synergistic effect on the risk of subsequent diarrhea.

Conclusion: Children with micronutrient deficiencies and in contact with animal had the highest risk of suffering subsequent diarrhea. Our findings support the current approach of providing multiple micronutrient supplements for the prevention of infection in order to reduce mortality in children.

Keywords: *Micronutrient deficiencies, Children, Diarrhea, Iran.*
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INTRODUCTION

Acute infectious diarrhea is still one of the most important causes of death in childhood (1). Malnutrition increases the morbidity and mortality of diarrhea through its negative impact on non-specific defence mechanisms and by altering the host immune mechanisms (2) and several studies have reported a strong correlation between the nutritional status of the child and the risk of subsequent diarrhea (3-5). Micronutrient deficiencies of vitamin A and zinc have also been shown to increase the child's susceptibility to acute and persistent diarrhea and supplementation of

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children with single micronutrients has been shown to reduce the incidence and hasten recovery from acute diarrhea episodes (6-8).

Although there is ample evidence that malnutrition and individual micronutrient deficiencies are associated with increased morbidity, most studies investigating these associations have focused on single micronutrients. There is thus a need to investigate if the presence of concurrent nutritional deficiencies increases the risk of subsequent diarrhea episodes in children.

PATIENTS and METHODS

Children less than 5 years old admitted to Hajar Hospital with a clinical diagnosis of acute diarrhea were enrolled systematically during workings days from October 2001 to August 2002. Hajar Hospital is a reference hospital serving the population of Chaharmahal va Bakhtiari province. Acute diarrhea was defined as the presence of three or more liquid or semi-liquid stools or a single watery stool per day of less than 14 days duration. After informed parental consent, parents were interviewed using standard questionnaires to obtain their socio-economic background, family characteristics and medical history. A total of 64 variables identified as risk factors in previous studies or considered to be potential risk factors within the local context were explored. The investigators did not modify the routine management of the children in the hospital and patients with clinically significant vitamin A deficiency should have received vitamin supplements. None of the children participating in the study, however, were deemed to require micronutrient supplements by the treating clinicians and the result of micronutrient concentration measurements were only available at the end of study.

After hospital discharge, children were followed up fortnightly by telephone, post or household visits for 14 consecutive weeks to assess if the child had experienced further diarrhea episodes. Parents not available during a scheduled visit were given new appointments and new attempts were made to contact them.

A child was classified as having recurrent diarrhea if the mother indicated that the child had a new episode 14 or more days after the initial acute diarrhea episode.

Blood samples (3 ml) were collected at the time of enrolment during the initial diarrhea episode to assess the micronutrient status of the children. Blood samples were left to clot, centrifuged at 1500 rpm for 5 minutes and the sera were stored at -20ºC. Serum samples were kept in dark-coloured safety tubes for the detection of vitamin A and E using the High-Performance Liquid Chromatography (HPLC) method, as described by Catignani et al (1983). Zinc, selenium and copper concentrations were measured by the Inductively Coupled Plasma–Mass Spectrometry (ICP –MS) method, as described by Delves et al (1997). Micronutrient measurements were performed at the end of the follow up period, once samples had been transferred to the U.K (Department of Medicine, University of Liverpool). Cut off values for each micronutrient were selected following internationally accepted cut off points to classify children as deficient or based on the statistical dispersion of the sample if reference cut off values were not available. Children with vitamin A and E concentrations <70 μmol/ l and <16 μmol/l were defined as vitamin A and E deficient, respectively (9-11). Zinc deficiency was defined as a plasma serum concentration <9.94 μmol/l (12). Copper and selenium deficiencies were defined as values of <1.5 μmol/l and <0.90 μmol/l. These cut off values were selected as there are no internationally recognised cut off values for these micronutrients (13,14). Stool samples were collected at the time of enrolment and tested for the presence of known pathogens.

The characteristics of the children and their micronutritional status at the time of admission

were correlated to the presence or absence of subsequent diarrhea episode using univariate analysis. A conservative approach was used to select variables for multivariate analysis and variables with p values < 0.20 were entered into a multiple logistic regression using the logistic regression programme of Epi 2002 to obtain adjusted odds ratios and 95% confidence intervals. Ethical issues in relation to all aspects were respected. Ethical approval has obtained from Research Ethic Committees of the Liverpool School of Tropical Medicine and the Shahrekord University of Medical Sciences.

RESULTS

Two hundred and eleven children were enrolled. Eighty-nine (42%) of the participants were female and 122 (58%) male. The acute diarrhea episodes of the children at the time of enrolment had lasted for a median of 3 days (range 1 to 13 days). Most children had diarrhea for one (14%), two (20%) or three days (18%) and only 10 (5%) children had diarrhea for 13 days. One hundred and thirty eight (65%) participants had vomited the week before enrolment.

One hundred and eighty four (87%) children had complete follow up and 27 (13%) had missed one or more appointments. Three out of the 27 children with incomplete follow up had missed one visit, 6 two visits, 7 three visits and 11 had missed ≥4 visits. The mean (SD) age on enrolment was 15.6 (12.5) with a range from 2 –59 months and the mean (SD) birth weight was 3.11 (0.56) Kgs. Only 19 (9%) children had a history of low birth weight. Children with complete follow up were compared to children who had missed one or more visits. Their medical history, clinical characteristics of the diarrhea episodes, laboratory results and family background were similar to those with incomplete follow up.

Fifty-eight (27%) children had subsequent diarrhea episodes during the follow up. Most children (44) had one episode, 12 had 2 episodes and 2 children had three or more episodes as shown in table 1.

Table 1. *Number of episode of subsequent diarrhea days with diarrhea and number of stools per day observed during the follow up period*

Number of		Number of children (%) (n=211)
Subsequent diarrhea episodes	0	153 (72%)
	1	44 (21%)
	2	12 (6%)
	3	1 (0.5%)
	4	1 (0.5%)
Days with diarrhea	0	153 (72%)
	1	34 (16%)
	2	12 (6%)
	3	8 (4%)
	4	1 (0.5%)
	≥5	3 (1.5%)
Watery stool per day	0	153(72%)
	1	6 (3%)
	2	6 (3%)
	3	15 (7%)
	4	18 (9%)
	≥5	6 (3%)
Unknown		7 (3%)

The mean (SD) duration of the initial acute diarrhea episode was 4.3 (3.3) days compared to 1.9 (1.6) days for subsequent episodes ($p<0.01$). The mean (SD) number of stools per day in the children with subsequent diarrhea episodes was 3.2 (1.2) compared to 7.1 (3.8) stools per day for the initial acute episodes ($p<0.01$). Thirty-four (59%) of the subsequent episodes lasted for one day, 12 (21%) for 2 days and 12 (21%) for 3 or more days. None of the children developed persistent diarrhea and the longest duration of subsequent diarrhea episodes was 10 days. Children with subsequent diarrhea were older than children without further episodes with a mean (SD) of 9.6 (15.3) versus 14.1 (10.9) months, respectively ($p<0.05$). Forty-eight (83%) of the children with subsequent diarrhea episodes returned to the health services compared to 51 (32%) of the children without subsequent diarrhea ($p<0.01$).

Table 2. *Characteristics of children with and without subsequent diarrhea*

Characteristics	Followed (n= 211)	Subsequent diarrhea		OR (95% CI)	P value
		With (n=58)	Without(n=153)		
Male/female (% female)	122/89 (42%)	35/23(40%)	87/66 (43%)	0.87 (0. 5-1.7)	0.76
Breast fed for ≤ 6 months	34 (11%)	9 (16%)	25 (16%)	0.96 (0.4- 2.4)	0.90
Age >12 months	118 (56%)	23 (40%)	95 (62%)	2.48 (1.3-4.9)	0.005*
Birth weight <2500	18 (9%)	4 (7%)	14 (9%)	1.34 (0.4- 5.2)	0.78
Weight-for-height z score < -1	87 (42%)	33 (57%)	54 (35%)	2.50 (1.3-4.9)	0.005*
Weight-for-age z score < -1	121 (57%)	41 (71%)	80 (52%)	2.20 (1.1-4.4)	0.02*
Family background					
Keep animals at home	56 (27%)	23 (38%)	33 (22%)	2.39 (1.2-4.8)	0.01*
Mother <20 years	5 (10%)	1 (2%)	14 (9%)	0.18 (0.1-1.3)	0.07*
Father has manual job	99 (47%)	34 (59%)	24 (16%)	1.90 (1- 3.7)	0.06*
Previous medical history					
Diarrhoea in the previous year	92(44%)	30 (52%)	62(41%)	0.64 (0.3-1.2)	0.20
Hospitalized in previous year	71 (34%)	25 (43%)	46 (30%)	1.80 (0.9-3.5)	0.09*
Initial diarrhea episode					
Stool ≤ 4 times	67 (32%)	16 (28%)	51 (33%)	0.77 (0.4-1.6)	0.55
With blood in stools	23 (11%)	4 (7%)	19 (12%)	0.52 (0.1- 1.7)	0.35
Duration ≤ 4 days	139 (66%)	35 (60%)	73 (48%)	1.65 (0.9-3.2)	0.15*
Fever (previous 5 days)	162 (77%)	48 (83%)	114 (75%)	1.60 (0.7- 2.4)	0.31
Vomiting (previous week)	138 (65%)	41 (71%)	97 (63%)	1.37 (0.7- 2.8)	0.43
Mild dehydration	108 (51%)	36 (62%)	87 (57%)	1.24 (0.6-2.4)	0.60
Presence of pathogens in stool	142 (67%)	22 (38%)	60 (39%)	1.06 (0.56-2.1)	0.98
Micronutrient status					
Selenium <0.90 µmol/l	131 (69%)	35 (60%)	96 (63%)	0.87 (0.4-1.7)	0.78
Vitamin A <0.70 µmol/l	57 (27%)	25 (43%)	32 (21%)	2.91 (1.4-5.9)	0.001*
Zinc <9.94 µmol/l	158 (75%)	49 (84%)	109 (71%)	2.92 (0.9-10.7)	0.07*
Copper <1.5 µmol/l	89 (45%)	61 (43%)	23 (55%)	0.62 (0.29-1.3)	0.24
Vitamin E <16 µmol/l	165 (87%)	124 (89%)	41 (82%)	1.7 (0.64- 4.5	0.34

* Selected for multivariate analysis

Table 3. *Multivariate analysis and adjusted odds ratios of the variables selected*

Variable	Subsequent diarrhoea		OR (95%CI)	P value	AOR (95%CI)	P value
	With	Without				
Age <12 months	23 (40%)	95 (62%)	2.48 (1.3-4.9)	0.005		
Weight-for-height z score	33 (57%)	54 (35%)	2.50 (1.3-4.9)	0.005		
Weight-for-age z score	41 (71%)	80 (52%)	2.20 (1.1-4.4)	0.02	2.5 (1.3-5.3)	0.01
Family background						
Keep animals at home	23 (38%)	33 (22%)	2.39 (1.2-4.8)	0.01	2.7 (1.3- 5.5)	0.01
Mother age <20 years	1 (2%)	14 (9%)	0.18 (0.1-1.3)	0.07		
Father has manual job	34 (59%)	24 (16%)	1.90 (1-3.7)	0.06		
Previous medical history						
Hospitalised in previous year	25 (41%)	46 (31%)	1.80 (0.9-3.5)	0.09		
Diarrhoea in previous year	32 (55%)	60 (38%)	0.64 (0.3-1.2)	0.20		
Index diarrhea episode						
Duration ≤ 4 days	35 (60%)	73 (48%)	1.65 (0.9-3.2)	0.15	2.7 (1.2-6.1)	0.01
Nutrition status						
Vitamin A <0.70 µmol/l	25 (43%)	32 (21%)	2.91 (1.4-5.9)	0.001	2.8 (1.3-5.8)	0.006
Zinc <9.94 µmol/l	49 (84%)	109 (71%)	2.92 (0.9-10)	0.07	3.9 (1.2-12.8)	0.04

A summary of the univariate analysis of the risk factors investigated is shown in table 2. Children with anthropometric z scores <-1 (weight-for height and weight- for-age) had an increased risk of subsequent diarrhea. Age <12 months had an inverse risk association, with younger infants experiencing less subsequent diarrhea than older children. Among the family background, children whose families kept animals at home and those who had a father working in manual activities had a higher risk of subsequent diarrhea, while children with young mothers (<20 years) had a lower risk. Children with a history of hospitalisation in the previous year were also more likely to experience subsequent diarrhea episodes following discharge from hospital. Seventy-six (36%) of the 211 children had rotavirus and 78 (37%) had other pathogens. Although the presence of rotavirus was associated with an increased risk of hospitalisation during the acute episodes on enrolment (15), the aetiology of the initial episodes was not associated with an increased risk of subsequent diarrhea. Among the micronutrients measured, vitamin A and zinc deficiency (<0.70 µmol/l and <9.94µmol/l respectively) were associated with an increased risk of subsequent diarrhea, while selenium, copper, and vitamin E deficiency were not associated.

Vitamin A<0.70 µmol/l, zinc<9.94 µmol/l and weight-for-age zscore<-1 were nutritional variables independently associated with recurrent diarrhea after the multivariate analysis, as shown in table 3 (AOR = 2.8, 3.9, and 2.5 respectively). There was also a negative association between the duration of the initial diarrhea episode and the risk of subsequent diarrhea and children with shorter diarrhea episodes on enrolment were more likely to have subsequent diarrhea (AOR =2.7). Of the variables related to the environment and family background, only ownership of animals (AOR= 2.7) reminded significant. The combination of the risk factors had synergistic effect. Children who had zinc and vitamin A deficiencies and kept animals at home had the highest risk of subsequent diarrhea (AOR of 9.2).

DISCUSSION

Despite the development of effective strategies for the management of acute diarrhea, this disease remains as one of the most important causes of death in childhood. Our study revealed that in this population, more than a quarter of the children with episodes of acute diarrhea severe enough to require hospitalisation, experience further diarrhea episodes after hospital discharge. The increased risk of recurrent diarrhea soon after an acute diarrhea episode has been recognised before, although there are surprisingly few studies that systemically investigate the risk factors for subsequent diarrhea. In Australia, aboriginal children and those who were severely dehydrated during the initial episodes, were more likely to suffer further episodes (16) and In the U.K, children attending health centres for acute diarrhea were six times more likely than population controls to have subsequent diarrhea episodes, with 10% of cases consulting their doctor in the 3 months following an initial episode and 2% being referred to the hospital (17). Information on the incidence and risk factors for recurrent diarrhea after an initial diarrhea episode in immunocompetent children in Africa or the Middle East is very scanty.

Diarrhea and other infections are often associated with malnutrition in a cycle that feeds each other. It has been estimated that 12 million children <5 years old die annually due to infection and malnutrition and about 70% these deaths are due to malnutrition(18-21). Malnutrition, particularly wasting, is a strong predictor of diarrheal disease duration, exacerbating nutritional faltering, thereby increasing the subsequent risk of death (22,23). The prevalence of micronutrients deficiencies in Iran, including zinc, vitamin A and

iodine deficiencies is high even thought malnutrition, as assessed by anthropometry, is less prevalent and few children have weight-for-height z scores <-1. This may be a reflection of the poor quality of their diets more than a shortage of food (24). There is however a body of evidence that supplementation with micronutrients reduces the incidence and duration of diarrhea in children (25,2). Community-based trials have been shown that zinc or vitamin A supplementation of children reduces the incidence of childhood diarrhea (8,27-30). In most, but not all studies, vitamin A supplementation has a synergistic effect when applied in combination with zinc supplements (31).

One limitation of our study is that micronutrient concentrations were measured at the time of the acute episode not at the time of discharge from hospital and plasma zinc and vitamin A concentrations change vary rapidly during the acute phase of infection. The micronutrient concentrations measured therefore might not reflect long term deficiencies before or after the acute diarrhea .Despite this limitation, our study revealed that low vitamin A and zinc concentrations at the time of admission to the hospital were still independent and synergistic factors increasing the child's risk of subsequent diarrhea, suggesting that the low concentrations had a prolonged effect that extended to the follow up period. In addition to the low micronutrient concentrations, malnutrition defined as a weight-for- age z score < -1, keeping animals at home and experiencing a short initial episode of acute diarrhea were independent risk factors.

An association between diarrhea and the presence of animals in the close environment has been reported for *Campylobacter* (26), *Cryptosporidium* (32), *Salmonella typhimurium* (33), *Cyclospora* (34) and other pathogens, and outbreaks of diarrhea have been described in visitors to farms (35,36). It is therefore likely that contact with animals in our setting is associated with a higher frequency of exposure to pathogens and to the lower hygiene standard of families residing in urban farms.

Although it was surprising that the aetiology of the initial episode was not a risk factor for subsequent diarrhea in our setting, this is in agreement with a report of Guinean children who had an increased incidence of subsequent diarrhea if the episode was caused by another pathogen other than rotavirus (37). Our children were not protected even if the initial diarrhea episode was due to rotavirus and further studies should be conducted in our setting. It is also interesting that children with shorter diarrhea episodes had a higher risk of subsequent diarrhea, independently of nutritional factors. This could be related to the infective dose of the organisms causing the diarrhea and children with severe episodes may have developed stronger immunological responses than children with mild infections.

Few studies to date have described the effect of a combination of factors on the risk of subsequent diarrhea. The aggregation of the factors had a synergistic effect on the risk of subsequent diarrhea and the children at the highest risk were those with a combination of micronutrient deficiencies and in contact with animals. Our findings support the current approached of providing multiple micronutrient supplementation for the prevention of infection and reduction of mortality in children.

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